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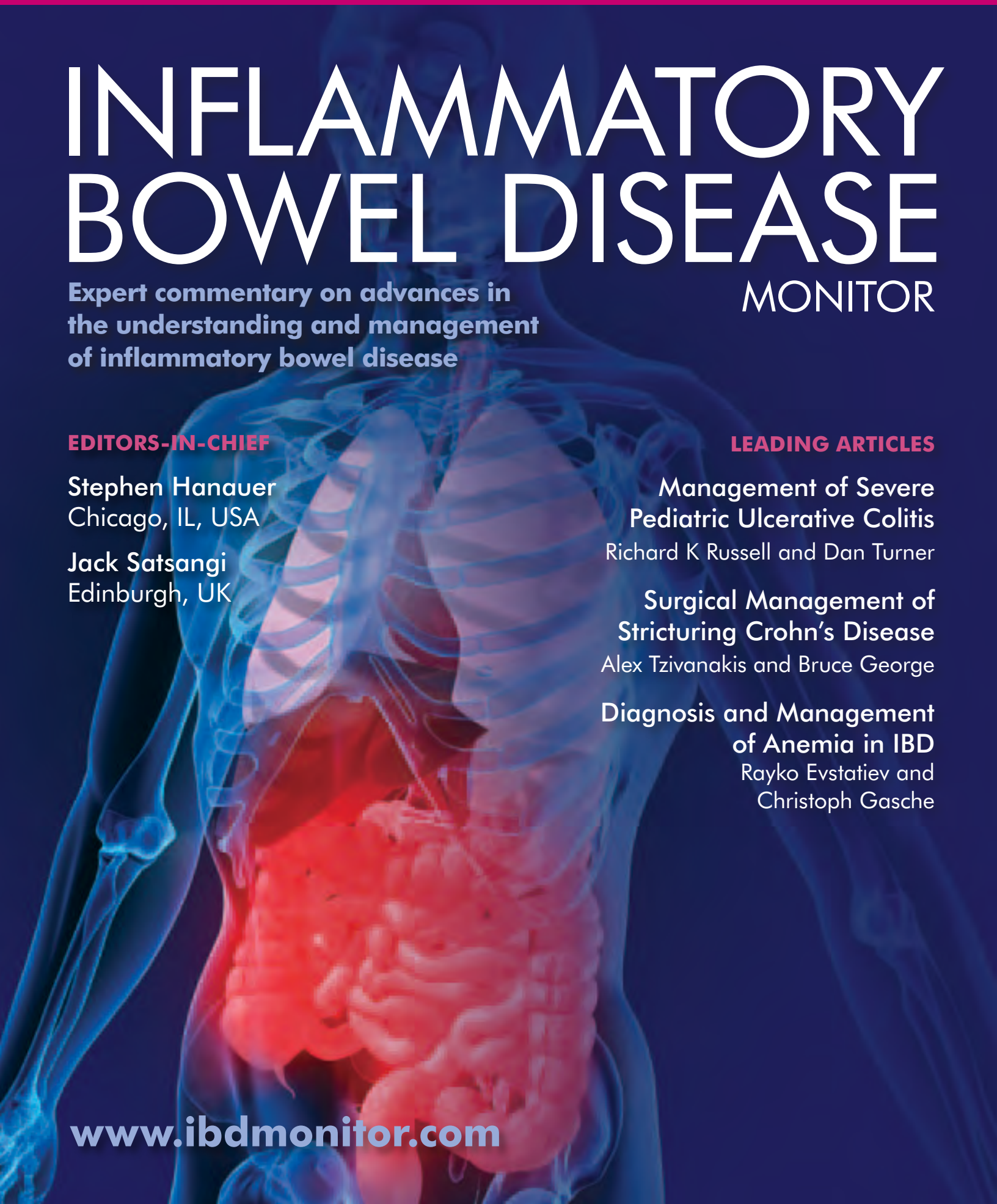

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Diagnosis and Management of Anemia in IBD

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With a prevalence of >30%, anemia is the most common extraintestinal complication of IBD. It impacts upon individual wellbeing, physical and mental performance, and, when severe, leads to hospitalization. Still, doctors do not recognize it early, and thus treatment is delayed. The pathogenesis of IBD-associated anemia is complex and goes hand-in-hand with iron deficiency, often combined with anemia of inflammation. International guidelines recommend regular screening for iron deficiency and anemia in IBD patients, with tests including full blood counts, C-reactive protein, and ferritin assessments. Further diagnostic workup is needed if iron deficiency or inflammation do not explain the cause of the anemia. Even in mild anemia, an adequate therapeutic response is warranted. Treatment goals are a sustained increase in hemoglobin and iron stores (for the prevention of the need for blood transfusions), a relief of anemia-related symptoms, and an improvement in quality of life. Iron deficiency may be substituted orally or intravenously. The use of oral iron preparations is limited to patients with mild anemia who tolerate oral iron therapy. The preferred route of iron supplementation in IBD is intravenous, as this does not carry the risk of potentiating IBD symptoms and provides fast iron repletion. Several studies have demonstrated that certain intravenous iron products are safe and effective. In cases of iron-refractory anemia, erythropoiesis-stimulating agents may improve the response. This review will emphasize the clinical impact of anemia in the setting of IBD and summarize the current state of the art in its diagnosis and management. *Inflamm Bowel Dis Monit* 2011;**11**(4):152–9.

Iron deficiency and anemia are the most common complications of IBD. Anemia affects more than 30% of patients at any time and thus is more frequent than other extraintestinal complications such as metabolic bone disease, urolithiasis, malignancy, opportunistic infections, or thromboembolism [1,2]. Anemia interferes with physical performance status, cognitive function, and quality of life (QoL), and leads to hospitalization and work disability. It is a hallmark of IBD activity, and hemoglobin or hematocrit are included in most clinical activity scores [3,4]. IBD-associated anemia may have multiple causes, but almost always presents with a certain degree of iron deficiency [5,6]. Anemia is a treatable condition, and its diagnosis should be followed by appropriate therapy. However, IBD-associated anemia is massively under-diagnosed and undertreated [7], probably due to a number of common misconceptions that trivialize the importance of anemia and negatively affect the clinical approach to this condition [8]. The purpose of the present work is to review the pathogenesis, diagnosis, and treatment of IBD-associated anemia in order to give the clinician an adequate perspective for the management of this commonly underestimated condition.

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Pathogenesis

Several pathogenetic mechanisms are involved in the development of anemia in IBD. In most cases, IBD-associated anemia is a combination of iron deficiency and anemia of chronic disease (ACD) [9]. Further causes include vitamin deficiencies, drug side effects, or hematological disorders.

Iron deficiency

Iron deficiency is by far the most common cause of anemia in IBD. Its prevalence can reach up to 90% in certain populations

[1]. In IBD, a negative iron balance occurs due to reduced iron intake, decreased iron absorption, and chronic bleeding. Overt and occult bleeding through the ulcerated intestinal mucosa is the most significant cause of a negative iron balance in IBD [9,10]. Dietary avoidance also plays a role in IBD-associated anemia. Approximately 1–2 mg/day of iron needs to be absorbed in order to overcome iron losses through minor bleeding, shedding of epithelial cells, and sweat [11]. The main source of iron is food, where it comes in two different forms: inorganic salts (ferrous [Fe^{2+}] or ferric [Fe^{3+}] iron) from plants or iron-fortified food and heme-bound iron mainly from meat [12]. The main site of iron absorption is the duodenum and the upper jejunum. Ferrous iron is taken up by the brush border of the enterocyte via the divalent metal transporter-1 (DMT-1; **Figure 1**) [13]. As most dietary iron exists in the ferric form, inorganic iron uptake is dependent on reduction to ferrous iron; this is performed by the brush border ferric reductase duodenal cytochrome B (DcytB) [14,15] as well as by reducing agents in the food, such as ascorbate. Moreover, iron chelation (by dietary substances such as phytic acid, tannins, or polyphenols) further limits iron uptake [12]. Thus, the bioavailability of inorganic iron is limited to only 2–20% [16].

Heme-bound iron is found in meat, poultry, and fish as hemoglobin or myoglobin. It is assumed that the heme-carrier protein-1 (HCP-1) shuttles heme into the enterocyte, where iron is released from the porphyrin ring (**Figure 1**). Compared with inorganic iron, heme shows better absorptive potential, ranging from 15–30% [17].

Dietary iron intake in IBD is low as some iron-rich and iron-fortified foods may exacerbate patients' symptoms, particularly abdominal pain and diarrhea [18,19]; in addition, the daily iron requirement is higher due to blood losses through the ulcerated gut mucosa. Intestinal absorption may also be impaired. The most obvious cause is duodenal Crohn's disease (L4 according to the Vienna and Montreal classification [20]), which is relatively rare (prevalence of <5% of all Crohn's disease cases). Nevertheless, impairment of iron absorption has been demonstrated even without upper gastrointestinal involvement [21]. The most likely mechanism involves the iron regulatory peptide hepcidin, which is upregulated in inflammation in a cytokine-dependent manner [22]. Hepcidin binds to the iron export protein ferroportin and leads to its degradation (**Figure 1**). Among the consequences of hepcidin-mediated ferroportin degradation is iron trapping within enterocytes and subsequent iron loss with the shedding of the iron-loaded cells. Hepcidin is markedly elevated in both Crohn's disease and ulcerative colitis (UC) and correlates well with markers of disease activity [23,24]. Upregulation of hepcidin in active IBD may also contribute to the lower efficacy of oral iron-replacement therapy.

Anemia of inflammation

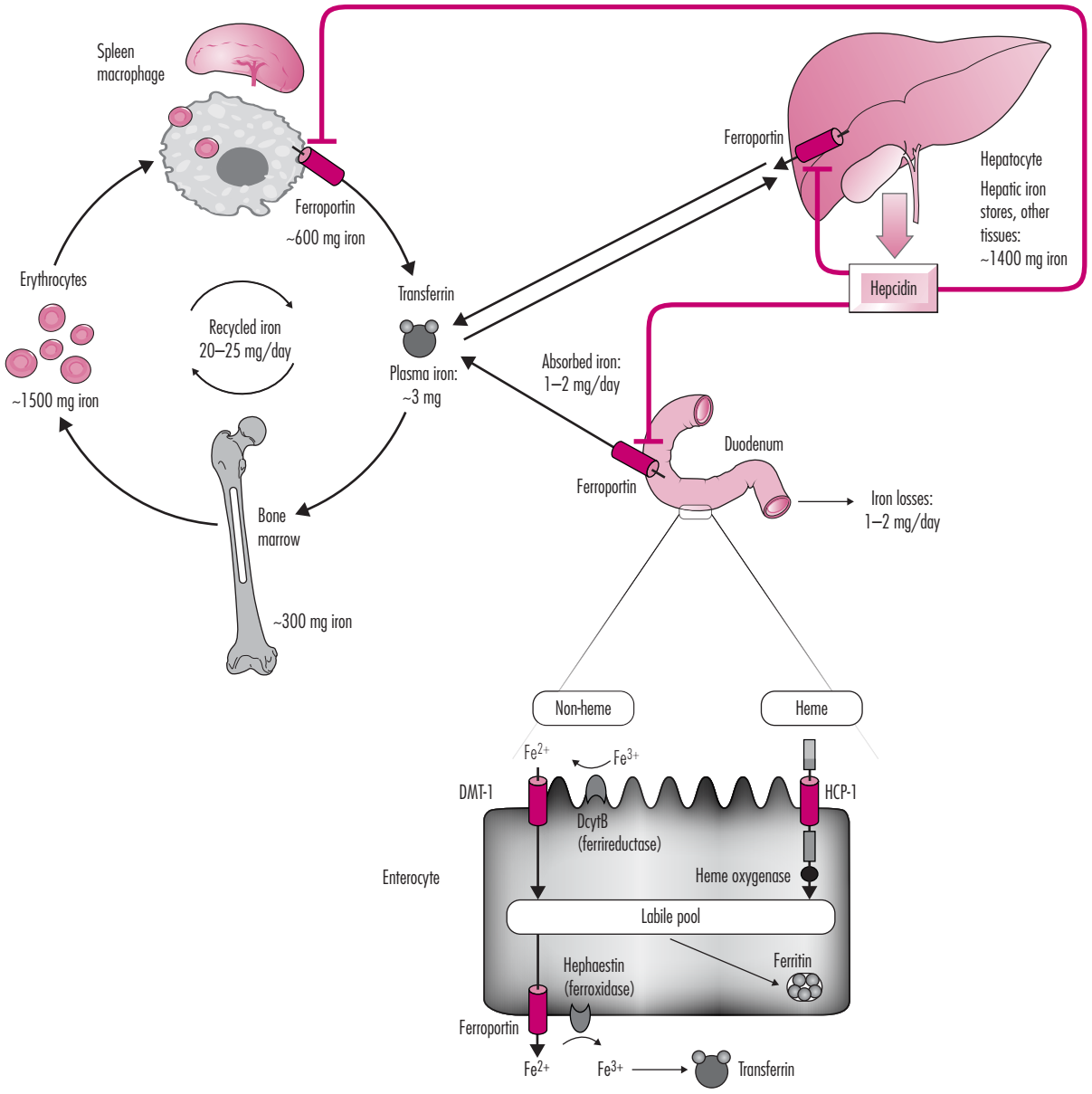
Anemia of inflammation (formerly termed ACD) constitutes the second most important mechanism in IBD-associated anemia and is the most significant cause of iron-refractory anemia in IBD [25]. It is a disorder of erythrocyte production due to acute or chronic immune activation and, besides IBD, may be found in acute or chronic infections, malignancies, and autoimmune disorders (reviewed in Weiss and Goodnough [26]). Although in some cases discrimination between pure iron deficiency anemia and ACD can be made, anemia in active IBD is virtually always a combination of both [9]. The development of ACD is mainly mediated by the retention of iron within cells of the monocyte–macrophage system (MMS) as well as in epithelial cells after absorption (as described above), and hence there is low systemic iron availability. Erythropoiesis is a highly dynamic process with an iron requirement of 20–25 mg/day, which exceeds the dietary iron uptake [13]. Therefore, most iron is recycled by the MMS, which phagocytoses senescent red cells and releases iron from hemoglobin in a controlled fashion. In ACD, proinflammatory cytokines such as interleukin-6 (IL-6) induce hepcidin production. By blocking the iron exporter ferroportin, hepcidin abrogates iron release from the MMS into the circulation; iron therefore remains trapped within phagocytes (**Figure 1**) [22]. Thus, ACD is characterized by normal or even elevated markers of body iron stores (ferritin) but low levels of transferrin-bound circulating iron (measured by transferrin saturation) as well as iron deficiency within the erythroid compartment (noticeable by elevations in the soluble transferrin receptor) [26].

An increase in pro-inflammatory cytokines can also directly impair erythroid precursor cells. Immune mediators such as interferons, tumor necrosis factor (TNF), and IL-1 downregulate erythropoietin receptor expression, reduce levels of other hematopoietic factors, and exert direct toxic effect via cytokine-inducible radicals. Furthermore, in ACD, erythropoietin production is inhibited and an adequate biological response to erythropoietic stimuli such as hypoxia is abrogated [26].

Further causes of IBD-associated anemia

Vitamin B_{12} deficiency can be a cause of IBD-associated anemia, with a prevalence of up to 22% [1,27–29]. Patients with ileal Crohn's disease or who have undergone ileal resection are specifically at risk [30]. Nevertheless, full-blown macrocytic anemia is relatively rare. Folate deficiency can play a role in adult IBD, specifically in patients who are on sulfasalazine or methotrexate treatment [1,28]. Interestingly, Heyman et al. showed elevated folate levels in pediatric IBD patients [31]; this finding remains unexplained at present. Vitamin deficiencies should be ruled out serologically and, if present, treated appropriately in patients with macrocytosis, unexplained anemia, or after ileal resection [9].

Figure 1. Body iron homeostasis. Dietary iron is absorbed in the upper gastrointestinal tract. Ferric iron salts utilize the DMT-1 transporter, whereas heme-bound iron is shuttled via HCP-1. Iron exits the enterocyte via ferroportin. Iron undergoes recycling through phagocytosis of senescent erythrocytes by cells of the monocyte–macrophage system, and subsequent release of hemoglobin-derived iron back into the circulation. The functions of the iron-regulating peptide hepcidin in binding to and degrading ferroportin, and its effects on intestinal iron absorption, release from iron stores, and inhibition of iron recycling, are also depicted.



DcytB: duodenal cytochrome B; DMT-1: divalent metal transporter-1; HCP-1: heme-carrier protein-1.

Some medications that are frequently used in the treatment of IBD may have a negative effect on erythropoiesis. Besides interfering with folate absorption, sulfasalazine may induce hemolysis or aplasia [1]. Thiopurines generally cause a mild bone marrow inhibition. In patients with variants of the metabolizing enzymes, severe bone marrow aplasia may occur [32]. Isolated anemia due to thiopurines is atypical. Bone marrow suppression and anemia is a well-known side effect of methotrexate. Anti-TNF therapy may lead to pancytopenia and bone marrow aplasia in rare cases but, in general, anti-TNF agents tend to ameliorate anemia by blocking one of the key pathogenic mechanisms of ACD [33,34].

Some hematological disorders may constitute rare causes of anemia in IBD. Hemolytic anemia is occasionally present in UC. It is rare in Crohn's disease where it is mostly associated with perinuclear antineutrophil cytoplasmic antibody (pANCA)-positivity and colonic disease. Glucose-6-phosphate dehydrogenase deficiency or thalassemias have been described

in IBD. Myelodysplastic syndrome may be a cause of anemia in patients aged >60 years [1,9,25].

Clinical presentation

Anemia presents with rather nonspecific symptoms such as fatigue, dizziness, tinnitus, headache, and shortness of breath that may be exacerbated during physical exercise [18,25]. Most of these symptoms are explained by reduced oxygen delivery to tissues. Compensatory shifting of blood from the splanchnic vessels may worsen perfusion of the intestine and change motility. In patients with cardiac comorbidity, anemia may reduce cardiac oxygen delivery, leading to heart failure [35,36]. Loss of libido and impotence can further impair QoL. Anemia affects physical performance, cognitive function, and QoL. Changes in QoL have been established in multiple studies (reviewed in Gisbert et al. [8]), and even patients with mild anemia can benefit from treatment [37]. Iron deficiency itself reduces proliferation of epithelial cells (this is known as Plummer–Vinson syndrome of the esophagus), but may also affect regeneration of tissue in inflamed areas of the small and large intestine. Hair loss, restless legs, brittle fingernails, and angular stomatitis are visible clinical findings [38]. Multiple aspects of cellular function including cell proliferation, growth, differentiation, myelinogenesis, immune function, energy metabolism, and biotransformation are impaired in iron deficiency [38,39]. In addition, iron deficiency anemia can lead to the development of reactive thrombocytosis [40,41], which may be associated with thromboembolic complications [42,43]. Thrombocytosis in IBD is considered not only to contribute to thromboembolism, but also to aggravate intestinal inflammation [44].

Diagnosis

Complete blood counts, C-reactive protein (CRP), and ferritin assessments are minimum requirements for the early detection of anemia, active inflammation, and iron deficiency, and should be assessed every 6–12 months in inactive disease and every 3 months in active IBD [10]. The World Health Organization (WHO) defines anemia as hemoglobin levels <12 g/dL for females and <13 g/dL for males [45]. These cutoffs are also acceptable for IBD patients at sea level. However, these ranges are not based on cohort studies. According to the NHANES-III (Third National Health and Nutrition Examination Survey), the mean hemoglobin level for male Caucasians between the ages of 20 and 60 years is 15.2 g/dL; for females aged between 20 and 50 years, it is 13.6 g/dL [46]. These may be considered the possible treatment targets (see below) [10]. For now, the proven treatment targets remain no anemia and no ferropenia.

Once anemia and iron deficiency have been diagnosed, treatment is straightforward. The most sensitive marker for iron deficiency is ferritin. There is little doubt that ferritin <30 µg/L corresponds to empty iron stores [47,48]. However, ferritin is an acute-phase marker and its levels are highly elevated in inflammation. In such cases, ferritin does not accurately reflect iron stores [26]. Patients with ferritin levels between 20 µg/L and 100 µg/L fall into a "grey" zone. In patients in remission, a ferritin value within this range may reflect adequate iron stores, whereas in active disease, these patients are very likely to be iron deficient. Therefore, several clinical studies, as well as international guidelines, use a cutoff of 100 µg/L or even higher to define iron deficiency and trigger iron-replacement therapy [9,49–51]. In cases in which active disease is present, additional parameters may be utilized to determine the status of iron stores and the extent of ACD. The presence of typical symptoms of iron deficiency (such as brittle hair and nails, and restless legs) may help to confirm the diagnosis of iron deficiency. Mean cellular volume (MCV) and mean cellular hemoglobin (MCH) levels may also be useful for verifying iron deficiency when ferritin levels are high, as iron-deficiency anemia typically represents a microcytotic, hypochromic anemia, as opposed to ACD, which can be normocytic and normochromic [10,26]. MCV and MCH parameters may be misleading, as they can lie within normal ranges even if iron deficiency is present. An increase in MCV may be a result of thiopurine therapy [52]. When iron deficiency is combined with vitamin B_{12} or folate deficiency, MCV and MCH may also be relatively high for the degree of iron deficiency [1].

Elevated CRP and erythrocyte sedimentation rate can be indicative for a high degree of inflammation and for the presence of ACD. Transferrin saturation <16% together with ferritin levels of 30–100 µg/L are associated with ACD overlapping with iron deficiency anemia, whereas ACD with adequate iron stores is likely when ferritin is >100 µg/dL and transferrin saturation is <16% [9,26]. The soluble transferrin receptor (sTfR) is also a useful marker that is elevated in iron-deficient erythropoiesis [53]. The sTfR/log ferritin ratio is potentially valuable for discriminating between iron deficiency (if the ratio is >2) and ACD (if the ratio is <1) [54]. Additional hematological parameters that may be utilized to identify iron deficiency are hypochromic red cells, zinc protoporphyrin, or reticulocyte hemoglobin concentration [10].

In macrocytotic cases or in patients with ferritin levels >100 µg/L, a diagnostic workup should rule out vitamin B_{12} or folate deficiency, hemolysis, or hemoglobionopathies [9,55,56]; however, a referral to a consultant hematologist may be required in such cases.

Therapy

All patients with IBD-associated anemia should receive appropriate treatment because even a mild decrease in

Table 1. Intravenous iron preparations.

	Trade names	Complex stability	Test dose	Recommended infusion dose	Infusion time	Risk of dextran-induced anaphylaxis
High molecular weight iron dextran	Dexferrum (Luitpold Pharmaceuticals)	Stable	Yes	1000 mg	360 min	Yes
Low molecular weight iron dextran	Infed, Cosmofer (Pharmacosmos)	Stable	Yes	1000 mg	360 min	Yes
Iron gluconate	Ferrlecit (Sanofi-Aventis)	Unstable	No	62.5–125 mg	60 min	No
Iron sucrose	Venofer (Vifor Pharma)	Semistable	Yes/no	200–500 mg	30–100 min	No
Ferric carboxymaltose	Ferinject (Vifor Pharma)	Stable	No	1000 mg	15 min	No
Iron isomaltoside 1000	Monofer (Pharmacosmos)	Stable	No	1000 mg	15–60 min	No

Data based on the relevant prescribing information documentation. Adapted with permission from Gasche et al. [8].

hemoglobin can impair QoL. The therapeutic goals in IBD-associated anemia are to increase the hemoglobin, serum ferritin, and transferrin saturation above the lower thresholds of normal, to prevent further reductions in hemoglobin, to avoid the use of blood transfusions, to relieve symptoms related to anemia, and to improve QoL [9]. Therefore, the generally accepted treatment targets are no anemia and no ferropenia. Published guidelines recommend that treatment of IBD-associated anemia should aim for the mean normal hemoglobin concentration (i.e. 15 g/dL for males and 13.5 g/dL for females) [10]. In other indications such as chronic kidney disease, lower target hemoglobin values (11–13 g/dL) are associated with better survival due to the increased risk of thromboembolic complications [57,58]. This risk may be attributed to the concomitant therapy with erythropoiesis-stimulating agents (ESAs) and to the comorbidity in these patients rather than the high hemoglobin itself, and it is unclear whether these concerns apply to the IBD population. Ferritin should be raised ideally to >100 µg/L, as low end-of-treatment ferritin levels predict the recurrence of iron deficiency and anemia [59]. Recurrence of anemia is very common in IBD patients and maintenance iron-replacement therapy might be necessary. As anemia is often a sign of subclinical IBD activity, especially in Crohn's disease, a diagnosis of anemia should also trigger an evaluation of disease activity and, if required, concomitant IBD therapy should be adjusted in order to prevent further intestinal blood and iron loss, and to reduce the degree of inflammation. If present, vitamin B_{12} and folic acid deficiencies should be treated [55,56]. A referral to a specialist hematologist is warranted if the cause of anemia is unclear, or if hemoglobin response is inadequate despite appropriate therapy.

Intravenous iron therapy

The most common cause of IBD-associated anemia is iron deficiency or a combination of iron deficiency and ACD; therefore, iron-replacement therapy is typically warranted. Current intravenous preparations on the market are ferric–carbohydrate complexes that differ in sugar moiety, complex stability, the maximal applicable dose of iron, the duration of infusions, and the need for an initial test dose (**Table 1**). Dextran-based intravenous iron preparations (high-molecular-weight iron-dextran and, more recently, low-molecular-weight iron-dextran) have been used effectively in IBD [47,60,61] but there is a certain risk of life-threatening anaphylactic reactions or skin necrosis after accidental paravenous application. The new generation of intravenous iron preparations (sucrose, carboxymaltose, and isomaltoside) has a considerably improved safety profile. Until recently, the iron dose was calculated by the Ganzoni formula, as follows: total iron deficit in mg = (body weight in kg × [target hemoglobin – actual hemoglobin in g/dL] × 0.24) + 500.

The Ganzoni formula, however, is inconvenient and underestimates the iron requirement [9,49,59]. A simplified dosing scheme based on hemoglobin and body weight (**Table 2**) has been evaluated prospectively for ferric carboxymaltose [49], and proved superior to the Ganzoni formula.

Absolute indications for intravenous iron therapy include non-response or intolerance to oral iron, severe anemia (hemoglobin <10 g/dL), active IBD, or concomitant therapy with ESAs [10]. Intravenous iron replacement has been shown to be efficacious and safe in numerous clinical trials, and it leads to a rapid hematological and QoL response [1,49–51,60,62]. Side effects are infrequent and may include a metallic taste during infusions, headache, or infusion-site reactions (including thrombophlebitis). As mentioned above, anaphylactic reactions may occur with dextran-containing preparations; a test dose ahead of the infusion should therefore be administered. Free iron may cause a capillary leak syndrome that can be mistaken for anaphylaxis (symptoms include hypotension, tachycardia, dyspnea, and peripheral edema). Such reactions arise when the transferrin saturation exceeds 100% and are attributed to a direct toxic effect of free iron. Because these reactions are not immune-mediated, they typically do not recur after

Table 2. Simplified dosing scheme for ferric carboxymaltose.

Hemoglobin (g/dL)	Body weight <70 kg	Body weight >70 kg
10 to normal	1000 mg (two infusions of 500 mg)	1500 mg (two infusions of 1000 mg and 500 mg)
7–10	1500 mg (three infusions of 500 mg)	2000 mg (two infusions of 1000 mg)

re-challenge. Ferric carboxymaltose may lead to a transient hypophosphatemia via an as yet unknown mechanism. When used appropriately, intravenous iron therapy should not cause iron overload, and elevation of ferritin above the upper limit of normal at up to 8 weeks after treatment is transient and does not reflect iron stores [63].

Oral iron therapy

Oral iron replacement preparations are cheap and convenient. Most marketed products are inorganic ferrous salts, sometimes combined with vitamin C. Oral iron replacement may be initialized in patients with mild anemia (hemoglobin >10 g/dL) and inactive disease. However, the use of oral iron in IBD is limited by several factors. Firstly, oral iron preparations are often poorly tolerated. Frequent side effects include worsening of IBD symptoms [64]. Although the bioavailability of oral iron is best when the preparations are taken on an empty stomach, gastrointestinal side effects limit this mode of application and it is therefore reasonable that iron preparations are taken with meals [10]. Most clinical studies conducted to date have been head-to-head comparisons with intravenous preparations; therefore, large doses of oral iron were administered [1,50,51]. As absorption of ingested iron is limited, it may be more appropriate to give lower doses of approximately 50–100 mg of elemental iron to minimize side effects [65]. Also, foods containing vitamin C enhance iron absorption [10,12]. A rise in hemoglobin under oral replacement is often slow [50,51,65,66]; thus, the treatment response should be closely monitored and, if required, a switch to intravenous replacement should be considered.

As absorption of dietary iron is limited, oral iron preparations lead to non-physiologically high iron concentrations within the intestinal lumen. Iron participates readily in redox reactions such as the Haber–Weiss and the Fenton reaction, leading to the production of reactive oxygen species. Luminal iron-induced oxidative stress may worsen inflammation and disease symptoms [64,67]. Werner et al. recently demonstrated that high luminal iron induces endoplasmic reticulum stress and leads to alterations in the gut microbiome in an animal model, thus aggravating disease activity [68]. In addition, insights from animal models imply that luminal iron may increase the incidence of colorectal tumors [69–73], and, although human studies conducted to date have been inconsistent [74–77], the use of oral iron preparations over periods of years should be avoided.

Erythropoiesis-stimulating agents

In some cases, replacement of iron alone fails to improve hemoglobin levels, most commonly due to the presence of ACD. Such patients may require an ESA in addition to iron replacement. Several trials have confirmed the efficacy and safety of ESAs in IBD-associated anemia (reviewed in Gasche et al. [9]). The addition of an ESA to the therapy regimen increases the response rate to 75–100%. There are no dose-finding trials in IBD and ESA doses that have been used in clinical trials are 150–200 U/kg of body weight three times per week for epoietin alfa, and 0.9 μg/kg body weight once weekly for darbepoietin alfa. Current practice recommendations are 30 000–40 000 U of epoietin once per week or 100–150 μg darbepoietin every 2 weeks. International guidelines favor the use of subcutaneous application [9]. In IBD, ESAs should always be combined with intravenous iron to avoid functional iron deficiency [78]. Unfortunately, because of the small market potential, the use of ESAs in IBD is not formally registered in most countries.

Blood transfusions

Chronic iron deficiency rarely warrants the transfusion of red blood cells. Young and otherwise healthy patients may tolerate hemoglobin levels as low as <6 g/dL. The indication for transfusions depends on the clinical situation (operation), the severity of anemia, rate of bleeding, hemodynamics, and cardiac comorbidity [9]. There are several reasons to limit the use of red blood cell transfusions to a minimum, including the risk of transfusion reactions, infections, costs, and hospitalization. Blood transfusions are not suitable for iron replacement as one pack contains just 200 mg of iron [9].

Conclusions

Anemia and iron deficiency are common conditions in IBD that have great impact on health and well-being. Despite international expert guidelines, appropriate anemia management has not been adopted in day-to-day practice [7]. Gastroenterologists seem to tolerate low hemoglobin levels better than their patients. Anemia can therefore remain unrecognized or neglected until a rock-bottom hemoglobin level triggers the use of blood transfusions. Yet, it is a simple medical condition that can be easily addressed with the appropriate attention.

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Disclosures

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